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Diastereoselective Trifluoroacetylation of Highly Substituted Pyrrolidines by a Dakin−West Process

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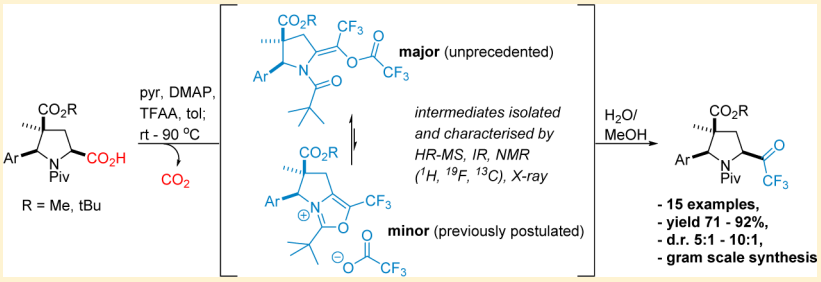
Supporting Information

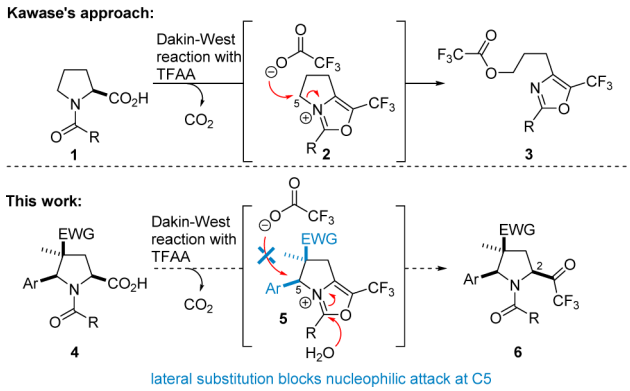


ABSTRACT: A robust approach allowing for the efficient trifluoroacetylation of a series of highly substituted pyrrolidines in a diastereoselective manner is reported. The transformation is based on a Dakin−West reaction of advanced pyrrolidine 2-carboxylic acid derivatives that can be assembled stereoselectively in four synthetic steps. Importantly, this work demonstrates how the introduction of lateral substituents on the pyrrolidine scaffold enables the generation of the desired trifluoroacetylation products, which was not possible previously due to the exclusive formation of trifluoromethylated oxazoles (vide infra). In the course of this work we succeeded for the first time in isolating and characterizing (HRMS, IR, ^{1}H, ^{13}C and ^{19}F NMR, X-ray) different intermediates of the Dakin−West reaction allowing us to probe its mechanism.

INTRODUCTION

The synthesis of chiral heterocycles containing fluorinated functionalities continues to be of great interest due to their importance in medicinal, agrochemical and material science applications.[1] In order to achieve this the fluorinated moiety can either be incorporated at an early stage in the synthesis or at the very end, the latter option often presenting several advantages as it allows for radiolabeling with ^{18}F[2] as well as late stage editing of structurally advanced architectures.[3] When surveying the literature we were intrigued by the absence of any reports detailing the constructive late stage incorporation of trifluoroacetyl groups into chiral pyrrolidines bearing variable substitution. Moreover, we noticed earlier reports by Kawase and co-workers[4] disclosing an interesting rearrangement process when subjecting *N*-acylated proline **1** to a Dakin−West protocol utilizing trifluoroacetic anhydride as the source of the trifluoroacetyl moiety which yielded trifluoromethylated oxazoles (**3**) exclusively (Scheme 1). The authors proposed a favorable nucleophilic attack at the C5 position of the bicyclic intermediate **2** leading to ring opening of the original pyrrolidine. On the basis of these results we hypothesized that introducing bulkier substituents around the vulnerable C5 position (**5**) should mitigate this undesired reaction pathway and allow for the alternative trifluoroacetylated pyrrolidines **6** instead.

Scheme 1. Kawase's Unsuccessful Dakin−West Approach and Our Hypothesis



RESULTS AND DISCUSSION

We thus set out to generate a selection of suitably substituted pyrrolidines by means of a diastereoselective [3 + 2]-cycloaddition approach[5] between different methacrylates (**10**) and azomethine ylides generated in situ from glycine imines (**9**), a process that had served us well in previous synthesis programmes.[6] Pleasingly, this approach allowed us to assemble

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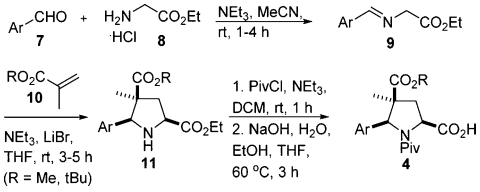
a series of trisubstituted pyrrolidines (**11**, d.r. > 10:1) bearing either methyl or *tert*-butyl esters at the quaternary carbon as well as a number of aromatic and heteroaromatic rings at the adjacent C5 position (Scheme 2).

Scheme 2. Four Step Synthesis of Substrates 4



The subsequent acylation of the pyrrolidine nitrogen with a pivaloyl (or related) group proceeded without problem. Ester hydrolysis under basic conditions rendered the desired acid substrates (**4**) as a suitable precursor for the subsequent Dakin–West reaction. Importantly, the saponification step can be accomplished regioselectively not affecting the quaternary methyl ester (Figure 2, substrates **4a–e**) or the stereochemical integrity of these advanced intermediates as evidenced by single crystal X-ray diffraction experiments (e.g., **4c**, Figure 1).

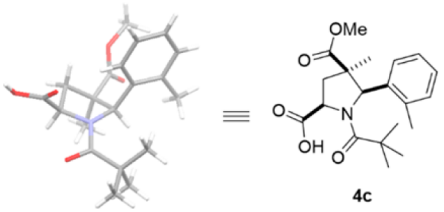
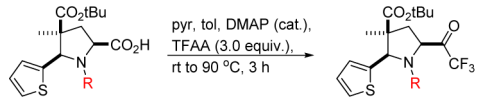


Figure 1. X-ray crystal structure of racemic acid **4c**.

Enabled by this short route the desired substrates **4a–o** bearing different ester and aryl appendages were prepared easily in high yields (see Figure 2) at scales of 10–20 mmol without recourse to chromatographic purifications (see SI for full details).

Having gained rapid access to these entities we proceeded by evaluating the impact of the substituent on the pyrrolidine nitrogen on the outcome of the Dakin–West reaction (Scheme 3). As such we dissolved acid substrates derived from the 2-thiophenylpyrrolidine scaffold **11j** bearing different substituents on nitrogen in a mixture of toluene and pyridine (1:1 by volume, 0.3 M), and then added a catalytic amount of DMAP and excess trifluoroacetic anhydride (TFAA, 3 equiv). After stirring this mixture at ambient temperature for 1 h the temperature was raised to 90 °C for 2 h prior to quenching of the reaction with a mixture of water and methanol (1:1 by volume). After extraction the crude product was analyzed by LC–MS and NMR (^{1}H, ^{19}F and COSY). It was immediately observed that unprotected systems (R = H) did not furnish significant amounts of the desired product (<10%), but led to substantial decomposition (>50%), a result that was paralleled by the simple *N*-acetylated substrates. Protecting the nitrogen with a more stable benzoyl group led to high conversion of the substrate to the Dakin–West product (>80%), however

Scheme 3. Initial Studies Evaluating the Impact of the Nitrogen Substituent R



12p, R = H; >50% decomposition
12q, R = Ac, >50% decomposition
12r, R = Bz, >80% conversion, d.r. 5:3
12j, R = Piv, full conversion, d.r. 9:1

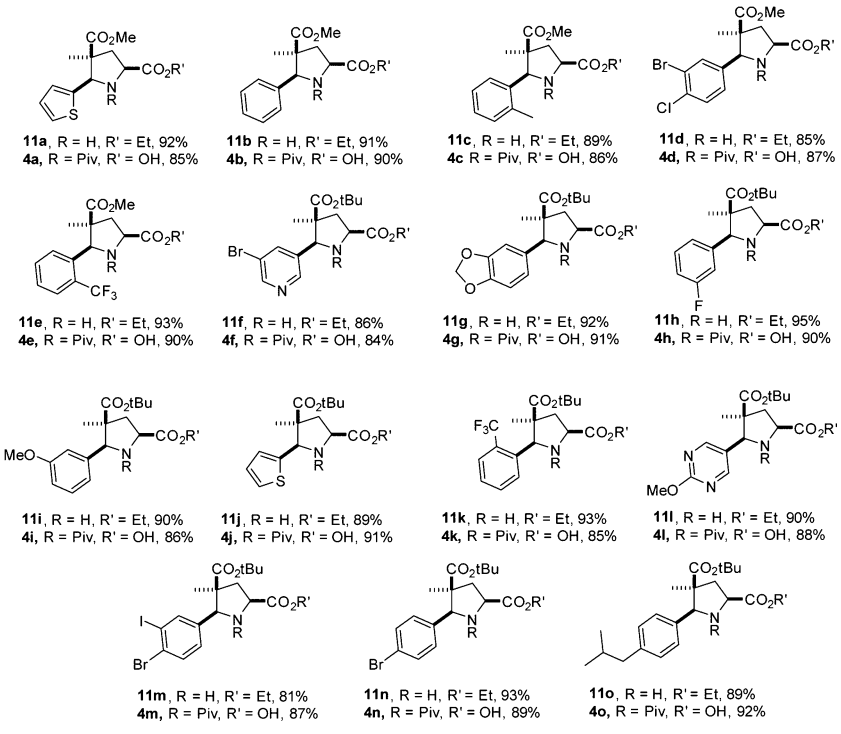


Figure 2. Structures and yields of isolated precursors **11** and **4**.

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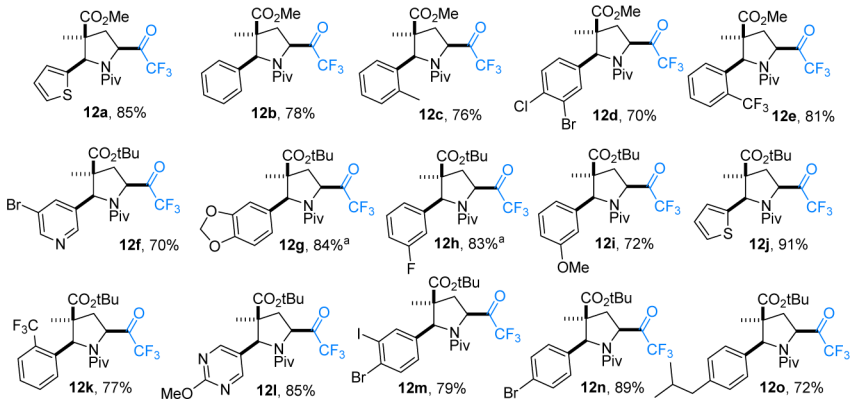

Figure 3. Trifluoroacetylated pyrrolidine products **12a–o**. ([a]Performed on 2 g scale).

yielding a mixture of diastereomers (d.r. 3:5) that was difficult to separate by silica column chromatography. Gratifyingly, the presence of a sterically more demanding pivaloyl group resulted not only in complete conversion of the substrate, but moreover furnished the desired trifluoroacetylated pyrrolidine product in high yield (91%) and good diastereoselectivity (d.r. 9:1). Consequently, we decided to proceed utilizing the *N*-pivaloylated substrates in our further studies.

Upon subjecting a collection of acid substrates **4** to the general Dakin–West conditions (Scheme 3) we were pleased to observe full and clean conversion of these starting materials to the desired trifluoroacetylated pyrrolidine products resulting in high isolated yields of the products (Figure 3). In addition a variety of different aryl systems were tolerated including heterocyclic systems (thienyl, pyridyl, pyrimidyl, methylenedioxyphenyl) and rings substituted with valuable halides enabling further functionalization reactions.

Beneficially, all of the Dakin–West products were generated with high diastereoselectivity (d.r. up to 10:1), indicating that protonation at C2 occurs predominantly from the convex face following hydrolysis of the putative bicyclic intermediate **5**. The assignment of the relative configuration was further supported by NOESY experiments as well as single crystal X-ray diffraction experiments (e.g., **12g**) as depicted in Figure 4.

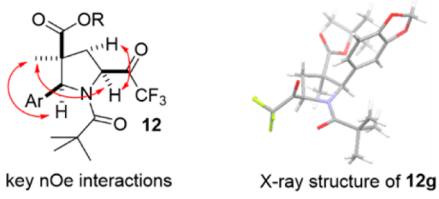

Figure 4. Key NOE interactions of compounds **12** and X-ray crystal structure of racemic **12g**.

A general trend regarding the diasteroselectivity of this Dakin–West process can be seen. The highest d.r. is obtained for substrates bearing either an unsubstituted or para-substituted aryl system (d.r. > 8:1), whereas meta-substituted systems typically show lower d.r. (6–7.5:1) followed by ortho-substitued cases (d.r. 5–5.5:1, Figure 5). While this pattern is not comprehensively understood, we ascribe this phenomenon to a torsional strain effect across the aryl-to-pyrrolidine bond resulting in less discriminating conformations that allow final protonation to also occur from the alternative face of these

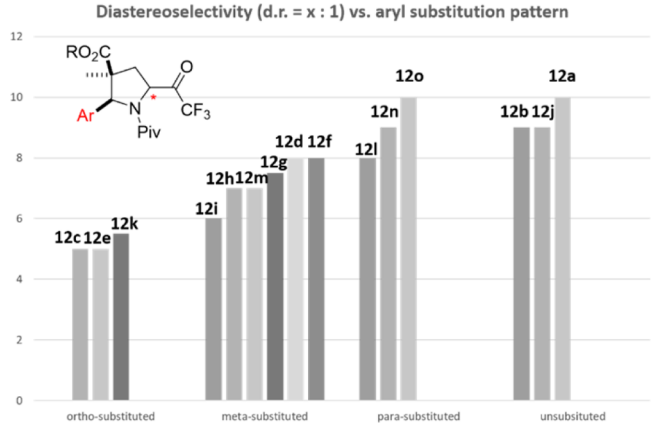

Figure 5. Correlation between diastereoselectivity and aryl substitution pattern.

structures. This effect is much more pronounced for systems bearing additional aryl substituents nearest the ring junction.

A final aspect of our endeavors concerned gaining a better understanding of the mechanism and intermediates formed during this Dakin–West type process (Scheme 4). It is widely accepted that under the standard reaction conditions a mixed anhydride (**13**) is formed when the acid substrate **4** reacts with TFAA or one of its derivatives resulting from nucleophilic catalysis via DMAP and/or pyridine.[7] Subsequently the nearby amide carbonyl can cyclize into this mixed anhydride expelling trifluoroacetate. The resulting bicyclic intermediate **14** likely exists in a zwitterionic form allowing further reaction with TFAA at the nucleophilic center adjacent to nitrogen. This process liberates a second equivalent of trifluoroacetate that can then attack the lactone carbonyl of **15**, eventually leading to an acyl transfer process accompanied by the release of CO_2 that is commonly observed through effervescence in the early stages of the reaction. Intermediate **17** could coexist with its ring closed form **5** either of which can then undergo hydrolysis through quenching of the reaction delivering the desired trifluoroacetyl product **12**.

In order to add further support to this mechanism we decided to identify isolable intermediates in order to analyze their structure. To this end we analyzed aliquots of several reactions of different substrates after 30 min at ambient temperature by ^{1}H and ^{19}F NMR. A consistent finding was that at this point all the starting material had been consumed and converted into a major new species characterized by the presence of two distinct fluorine environments (typically at

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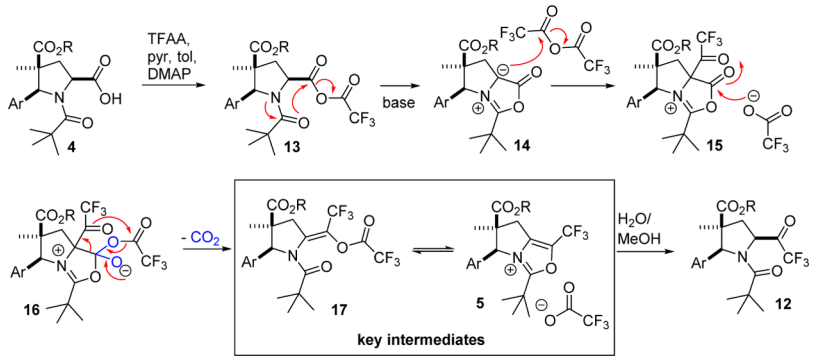
Scheme 4. Postulated Reaction Mechanism



−61 and −74 ppm). Upon heating the reaction mixtures to 90 °C no significant change in the composition of the crude product was observed by NMR. Although this material proved prone to hydrolysis generating the final reaction products **12**, we were able to use flash column chromatography for its purification enabling further analysis by ^{13}C NMR and X-ray crystallography. Crucially the latter proved the presence of a monocyclic species possessing a *Z*-configured carbon−carbon double bond with an enoxy trifluoroacetate moiety that would explain its facile hydrolysis rendering the final trifluoroacetyl products **12**. The single crystal X-ray structure of **17h** (Ar = 3-fluorophenyl) confirms this connectivity (Figure 6) and highlights the presence of two rotameric molecules in the unit cell.

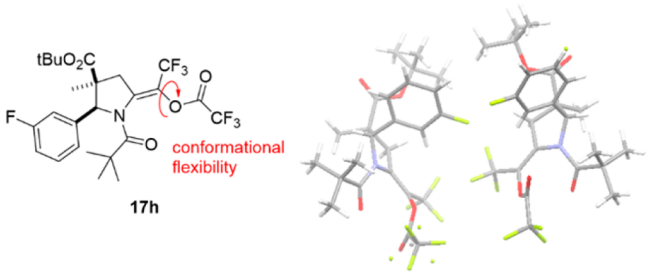


Figure 6. X-ray crystal structure of **17h**.

While the existence of this intermediate (**17**) can be accounted for by our proposed mechanism (Scheme 4) we are unaware of any previous reports relating to this being the predominant intermediate in the Dakin−West reaction.[8,9] Moreover, as bicyclic oxazolium-type intermediates like **5** are commonly proposed we attempted to find evidence for their existence. Although several efforts to identify this species were unsuccessful we eventually observed a second intermediate by ^{1}H NMR when employing substrate **4g** bearing a piperonyl substituent. In this case we were able to isolate sufficient quantities of clean material from silica column chromatography (∼100 mg, ∼10% yield[10]). Analyzing this purified material by various NMR techniques indicated a structure consistent with intermediate **5**. Furthermore, the ^{1}H NMR spectrum of intermediate **5g** (Ar = piperonyl) is distinctly different from the corresponding trifluoroacetyl pyrrolidine **12g** in that both the methylene protons (*3a*,*3b*) and the methine proton (5) are downfield shifted by ∼1 ppm, the latter to a larger extent as it is benzylic and hence more acidic (Figure 7).

The fact that upon hydrolysis of this species (**5g**) a single diastereomer at the benzylic position is obtained indicates that the adjacent quaternary carbon is imposing the overall diastereocontrol despite a mixture of C5-epimers being observed by NMR for this intermediate (d.r. = 3.6:1). The identity of this ionic species was further confirmed by HRMS (for the cation) and ^{19}F and ^{13}C NMR (for cation and trifluoroacetate anion). On the basis of this evidence we

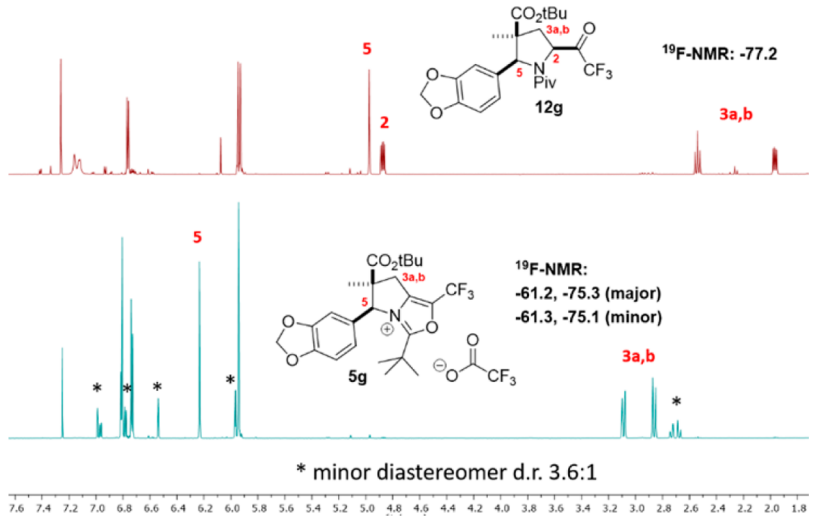


Figure 7. ^{1}H NMR stack plot of **12g** and **5g** ($CDCl_3$, 700 MHz, 1.7−7.7 ppm).

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conclude that the predominant intermediate in this type of Dakin–West reaction is actually the enoxy trifluoroacetate **17**, whereas the bicyclic oxazolium species **5** is either a minor, less stable intermediate, or coexists in equilibrium with **17** as the major isolable constituent. In either case, both intermediates **17** and **5** furnish the desired reaction product **12** upon hydrolysis.

Despite a plethora of mechanistic studies on the Dakin–West reaction[7,9] this current study appears to be the first report of fully characterizing several of its key intermediates which therefore supports our mechanistic rationale. Furthermore, our report shows that bicyclic intermediates such as **5**, which have been postulated, are indeed productive intermediates generating the desired Dakin–West products, although a further intermediate (i.e., **17**) appears to play a preeminent role in the reaction mechanism yielding the desired trifluoroacetyl products **12**.

CONCLUSION

In summary, we have developed an efficient access into various trifluoroacetyl pyrrolidines bearing variable substituents. Importantly, lateral substitution enables the desired entities to be generated through a Dakin–West reaction eliminating alternative reaction pathways that previously led to trisubstituted oxazole products. The trifluoroacetyl pyrrolidines were all obtained in high yields (70–91%) and with high diastereoselectivity (d.r. 5:1 to 10:1) that was found to be finely controlled by the substitution pattern on the aryl moiety in the 5-position of the pyrrolidine ring. We have also succeeded in isolating and characterizing two key intermediates of this Dakin–West reaction process, namely the originally proposed oxazolium species **5** and a new enoxy trifluoroacetate species **17**. While the former appears to be a minor and more obscure intermediate, the latter was consistently found to form rapidly yielding the desired reaction products upon hydrolysis. This could be rationalized for by the use of secondary amino acids which follow a slightly different reaction mechanism than primary amines in the classical Dakin–West reaction.

Ultimately, we believe that this efficient entry into a new class of pyrrolidines bearing a chiral fluorinated moiety is a valuable method for the late stage trifluoroacetylation and will find several applications in medicinal chemistry.

EXPERIMENTAL SECTION

General Experimental for Preparation of Compounds 11a–o. To a solution of aldehyde **7** (1.0 equiv) in MeCN (1 M) was added glycine ethyl ester hydrochloride (**8**, 1.3 equiv) and triethylamine (1.3 equiv). The resulting suspension was stirred at room temperature until complete consumption of the aldehyde was observed (TLC or ^{1}H NMR, 1–4 h). After evaporation of the solvent the crude material was partitioned between EtOAc (20 mL) and water (20 mL) and extracted three times. The combined organic layers were dried over sodium sulfate, filtered and evaporated to give imine **9** typically as a colorless oil. To a solution of this imine (1.0 equiv) in THF (1 M) was added triethylamine (1.2 equiv), the desired methacrylate ester (**10**, 1.2 equiv) and LiBr (1.2 equiv) resulting in a solution color change to yellow. This mixture was stirred at room temperature until complete consumption of the imine was observed (TLC or ^{1}H NMR, 2–6 h). Evaporation of the volatiles followed by aqueous extraction (20 mL EtOAc, 20 mL water, three times) yielded the desired pyrrolidine cycloadduct after drying and removal of solvent. These pyrrolidine products (**11**) were typically isolated as oils with a purity >90% (d.r. ~ 10:1) and can be carried forward without further purification.

*Rac-(2S,4S,5S)-2-Ethyl 4-methyl-5-(thiophen-2-yl)pyrrolidine-2,4-dicarboxylate, (**11a**).* Yield: 92% (2.7 g; 9.2 mmol). Appearance: yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 5.0, 1.3 Hz, 1H), 6.90–6.94 (m, 1H), 6.89 (dd, J = 4.9, 3.6 Hz, 1H), 4.25 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.96 (dd, J = 9.1, 7.2 Hz, 1H), 3.36 (s, 3H), 2.97 (br s, 1H), 2.65 (dd, J = 13.1, 7.2 Hz, 1H), 2.09 (dd, J = 13.4, 9.1 Hz, 1H), 1.39 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5 (C), 173.3 (C), 142.2 (C), 126.6 (CH), 124.34 (CH), 124.28 (CH), 69.3 (CH), 61.1 (CH_2), 58.9 (CH), 54.5 (C), 51.6 (CH_3), 41.1 (CH_2), 22.2 (CH_3), 14.2 (CH_3). IR (neat, cm^{-1}) 2980 (w), 1729 (s), 1434 (w), 1378 (w), 1200 (s), 1136 (m), 1109 (m), 1034 (m), 990 (m), 905 (m), 851 (m), 699 (s). LC–MS (ESI) m/z = 298.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{14}H_{20}NSO_4$ 298.1113; found 298.1107 (Δ 2.0 ppm).

*Rac-(2S,4S,5S)-2-Ethyl 4-methyl-5-phenylpyrrolidine-2,4-dicarboxylate, (**11b**).* Yield: 91% (4.0 g; 13.7 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.34 (m, 5H), 4.30 (q, J = 7.2 Hz, 2H), 4.07 (s, 1H), 4.04 (dd, J = 9.0, 7.0 Hz, 1H), 3.54 (br s, 1H), 3.24 (s, 3H), 2.73 (dd, J = 13.2, 7.0 Hz, 1H), 2.13 (dd, J = 13.2, 9.0 Hz, 1H), 1.42 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (C), 173.7 (C), 138.6 (C), 128.2 (2CH), 127.9 (CH), 126.7 (2CH), 73.9 (CH), 61.2 (CH_2), 59.0 (CH), 54.8 (C), 51.3 (CH_3), 41.5 (CH_2), 22.6 (CH_3), 14.3 (CH_3). IR (neat, cm^{-1}) 2981 (w), 1728 (s), 1455 (m), 1378 (m), 1201 (s), 1140 (m), 1109 (m), 1033 (m), 748 (m), 700 (s). LC–MS (ESI) m/z = 292.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{16}H_{22}NO_4$ 292.1549; found 292.1560 (Δ 3.8 ppm).

*Rac-(2S,4S,5S)-2-Ethyl 4-methyl-5-(o-tolyl)pyrrolidine-2,4-dicarboxylate, (**11c**).* Yield: 89% (2.7 g; 8.9 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 1H), 7.05–7.15 (m, 3H), 4.45 (s, 1H), 4.25 (qd, J = 7.2, 2.1 Hz, 2H), 3.98 (app t, J = 8.1 Hz, 1H), 3.16 (s, 3H), 2.75 (dd, J = 13.1, 8.2 Hz, 1H), 2.65 (br s, 1H), 2.36 (s, 3H), 2.04 (dd, J = 13.1, 8.1 Hz, 1H), 1.41 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (C), 173.8 (C), 138.2 (C), 136.1 (C), 130.3 (CH), 127.3 (CH), 126.0 (CH), 125.8 (CH), 68.4 (CH), 61.1 (CH_2), 59.3 (CH), 55.6 (C), 51.3 (CH_3), 41.4 (CH_2), 23.6 (CH_3), 20.1 (CH_3), 14.3 (CH_3). IR (neat, cm^{-1}) 2950 (w), 1727 (s), 1463 (m), 1379 (m), 1208 (s), 1118 (m), 1033 (m), 752 (s). LC–MS (ESI) m/z = 306.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{17}H_{24}NO_4$ 306.1705; found 306.1719 (Δ 4.6 ppm).

*Rac-(2S,4S,5S)-2-Ethyl 4-methyl 5-(3-bromo-4-chlorophenyl)4-methylpyrrolidine-2,4-dicarboxylate, (**11d**).* Yield: 85% (3.4 g; 8.5 mmol). Appearance: yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.20 (dd, J = 8.3, 2.1 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 4.01 (s, 1H), 3.99 (app t, J = 8.8 Hz, 1H), 3.31 (s, 3H), 2.69 (dd, J = 13.3, 7.5 Hz, 1H), 2.08 (dd, J = 13.3, 8.7 Hz, 1H), 1.39 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H) . ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 173.6 (C), 139.9 (C), 133.6 (C), 132.2 (CH), 129.9 (CH), 127.0 (CH), 122.1 (C), 72.3 (CH), 61.2 (CH_2), 58.8 (CH), 54.7 (C), 51.6 (CH_3), 40.6 (CH_2), 22.8 (CH_3), 14.3 (CH_3). IR (neat, cm^{-1}) 2982 (w), 1728 (s), 1464 (m), 1199 (s), 1110 (s), 1023 (s), 909 (m), 823 (m), 730 (s), 663 (m). LC–MS (ESI) m/z = 404.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{16}H_{20}NO_4BrCl$ 404.0264; found 404.0270 (Δ 1.5 ppm).

*Rac-(2S,4S,5S)-2-Ethyl 4-methyl-5-(2-(trifluoromethyl)phenyl)-pyrrolidine-2,4-dicarboxylate, (**11e**).* Yield: 93% (3.3 g; 9.3 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.63 (m, 2H), 7.50 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 4.53 (s, 1H), 4.25 (dq, J = 7.2, 2.0 Hz, 2H), 4.00 (dd, J = 9.3, 7.3 Hz, 1H), 3.15 (s, 3H), 2.86 (dd, J = 13.0, 9.2 Hz, 1H), 2.62 (br s, 1H), 2.08 (dd, J = 13.0, 7.3 Hz, 1H), 1.42 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C), 173.5 (C), 140.4 (C), 131.7 (CH), 128.9 (CH), 128.5 (C, q, J = 30 Hz), 127.5 (CH), 125.5 (CH, q, J = 6 Hz), 124.2 (CF_3, q, J = 275 Hz), 67.2 (CH), 61.2 (CH_2), 59.0 (CH), 55.6 (C), 51.4 (CH_3), 41.2 (CH_2), 24.2 (CH_3), 14.2 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.8. IR (neat, cm^{-1}) 2984 (w), 2952 (w), 1730 (s), 1455 (m), 1310 (s), 1243 (m), 1205 (m), 1154 (s), 1119 (s), 1061 (m), 1035 (s), 769

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(s), 658 (m). LC−MS (ESI) m/z = 360.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{17}H_{21}NO_4F_3$ 360.1423; found 360.1431 (Δ 2.2 ppm).

*Rac-(2S,4S,5S)-tert-Butyl 2-ethyl 5-(5-bromopyridin-3-yl)-4-methylpyrrolidine-2,4-dicarboxylate, (**11f**).* Yield: 86% (3.5 g; 8.6 mmol). Appearance: yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 7.91 (t, J = 2.1 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.04 (s, 1H), 3.98 (t, J = 8.4 Hz, 1H), 2.63 (dd, J = 13.2, 8.8 Hz, 1H), 2.06 (dd, J = 13.2, 8.1 Hz, 1H), 1.42 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 172.6 (C), 149.8 (CH), 147.3 (CH), 138.0 (C), 137.5 (CH), 120.6 (C), 81.4 (C), 69.5 (CH), 61.3 (CH_2), 58.7 (CH), 55.0 (C), 40.8 (CH_2), 27.6 ($3CH_3$), 24.1 (CH_3), 14.2 (CH_3). IR (neat, cm^{-1}) 2978 (m), 1722 (s), 1451 (w), 1422 (m), 1368 (m), 1249 (m), 1201 (m), 1152 (s), 1110 (m), 1038 (M), 1021 (m), 847 (m), 707 (m). LC−MS (ESI) m/z = 413.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{18}H_{26}N_2O_4Br$ 413.1076; found 413.1087 (Δ 2.7 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpyrrolidine-2,4-dicarboxylate (**11g**).* Yield: 92% (3.5 g; 9.2 mmol). Appearance: pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J = 1.8 Hz, 1H), 6.78 (dd, J = 8.1, 1.8 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 5.89 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.94 (s, 1H), 3.93 (app t, J = 8.6 Hz, 1H), 2.72 (br s, 1H), 2.58 (dd, J = 13.1, 8.8 Hz, 1H), 2.03 (dd, J = 12.8, 8.2 Hz, 1H), 1.38 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C), 173.4 (C), 147.4 (C), 146.9 (C), 133.9 (C), 120.6 (CH), 108.0 (CH), 107.8 (CH), 100.9 (CH_2), 80.6 (C), 72.8 (CH), 61.1 (CH_2), 58.8 (CH), 55.0 (C), 41.7 (CH_2), 27.6 ($3CH_3$), 24.2 (CH_3), 14.2 (CH_3). IR (neat, cm^{-1}) 2978 (w), 1720 (s), 1488 (m), 1445 (m), 1367 (m), 1238 (s), 1195 (s), 1152 (s), 1036 (s), 933 (m), 849 (m), 808 (m), 732 (m). LC−MS (ESI) m/z = 378.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{20}H_{28}NO_6$ 378.1917; found 378.1915 (Δ 0.5 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl 5-(3-fluorophenyl)-4-methylpyrrolidine-2,4-dicarboxylate, (**11h**).* Yield: 95% (6.7 g; 19.0 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (td, J = 6.0, 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.09 (dt, J = 10.0, 12.0 Hz, 1H), 6.94 (tdd, J = 8.0, 2.6, 1.0 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.04 (s, 1H), 3.98 (app t, J = 8.6 Hz, 1H), 2.62 (dd, J = 13.1 8.8 Hz, 1H), 2.07 (dd, J = 13.1, 8.2 Hz, 1H), 1.45 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C), 173.2 (C), 162.6 (CF, J = 246 Hz), 142.7 (C, J = 7 Hz), 129.5 (CH, d, J = 8 Hz), 122.9 (CH, d, J = 3 Hz), 114.5 (CH, d, J = 13 Hz), 114.3 (CH, d, J = 12 Hz), 80.8 (C), 72.4 (CH), 61.2 (CH_2), 58.9 (CH), 55.0 (C), 41.8 (CH_2), 27.5 ($3CH_3$), 24.3 (CH_3), 14.3 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.5. IR (neat, cm^{-1}) 2978 (w), 1722 (s), 1590 (m), 1451 (m), 1368 (m), 1251 (s), 1151 (s), 1112 (s), 1033 (s), 848 (m), 791 (s), 693 (m). LC−MS (ESI) m/z = 352.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{19}H_{27}NO_4F$ 352.1924; found 352.1923 (Δ 0.3 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl 5-(3-methoxyphenyl)-4-methylpyrrolidine-2,4-dicarboxylate, (**11i**).* Yield: 90% (3.9 g; 10.8 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, J = 8.1 Hz, 1H), 6.93−6.98 (m, 2H), 6.77 (ddd, J = 8.2, 7.4, 1.1 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.01 (s, 1H), 3.96 (dd, J = 8.9, 8.1 Hz, 1H), 3.78 (s, 3H), 2.83 (br s, 1H), 2.60 (dd, J = 13.0, 8.9 Hz, 1H), 2.06 (dd, J = 13.0, 8.1 Hz, 1H), 1.44 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C), 173.4 (C), 159.4 (C), 141.6 (C), 129.0 (CH), 119.6 (CH), 113.0 (CH), 112.9 (CH), 80.5 (C), 72.9 (CH), 61.1 (CH_2), 59.0 (CH), 55.2 (CH_3), 55.1 (C), 42.2 (CH_2), 27.5 ($3CH_3$), 24.4 (CH_3), 14.3 (CH_3). IR (neat, cm^{-1}) 2978 (w), 1721 (s), 1602 (m), 1456 (m), 1367 (m), 1251 (s), 1152 (s), 1115 (s), 1040 (s), 849 (m), 784 (m), 697 (m). LC−MS (ESI) m/z = 364.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{20}H_{30}NO_5$ 364.2124; found 364.2112 (Δ 3.3 ppm).

*Rac-(2S,4S,5R)-4-tert-Butyl 2-ethyl 4-methyl-5-(thiophen-2-yl)-pyrrolidine-2,4-dicarboxylate, (**11j**).* Yield: 89% (4.5 g; 13.4 mmol). Appearance: yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J = 5.1, 1.3 Hz, 1H), 6.95 (dt, J = 3.6, 1.1 Hz, 1H), 6.91 (dd, J = 5.1, 3.6 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.22 (s, 1H), 3.98 (app t, J = 8.6 Hz, 1H), 2.88 (br s, 1H), 2.57 (dd, J = 13.3, 8.5 Hz, 1H), 2.12 (dd, J = 13.3, 8.7 Hz, 1H), 1.46 (s, 3H), 1.28 (s, 9H), 1.13 (t, J = 7.2 Hz, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 173.2 (C), 142.7 (C), 126.5 (CH), 124.3 (CH), 124.0 (CH), 80.9 (C), 68.53 (CH), 61.2 (CH_2), 58.9 (CH), 54.9 (C), 42.2 (CH_2), 27.5 ($3CH_3$), 23.4 (CH_3), 14.2 (CH_3). IR (neat, cm^{-1}) 2977 (w), 1722 (s), 1449 (w), 1368 (m), 1247 (m), 1150 (s), 1034 (m), 848 (m), 735 (m), 697 (s). LC−MS (ESI) m/z = 340.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{17}H_{26}NO_4S$ 340.1583; found 340.1595 (Δ 3.5 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl-4-methyl-5-(2-(trifluoromethyl)phenyl)pyrrolidine-2,4-dicarboxylate, (**11k**).* Yield: 93% (3.7 g; 9.3 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 4.51 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.99 (dd, J = 6.5, 11.2 Hz, 1H), 2.79 (dd, J = 12.8, 11.2 Hz, 1H), 2.55 (br s, 1H), 2.04 (dd, J = 6.1, 13.2 Hz, 1H), 1.46 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 0.95 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C), 173.0 (C), 142.4 (C), 132.2 (CH), 129.7 (CH), 128.6 (C, q, J = 30 Hz), 127.2 (CH), 125.1 (CH, q, J = 6 Hz), 124.3 (CF_3, q, J = 275 Hz), 80.5 (C), 66.2 (CH), 61.1 (CH_2), 59.0 (CH), 56.2 (C), 41.1 (C), 27.2 ($3CH_3$), 26.1 (CH_3), 14.2 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.8. IR (neat, cm^{-1}) 2981 (w), 1722 (s), 1456 (m), 1368 (m), 1310 (s), 1251 (m), 1152 (s), 1121 (s), 1060 (m), 1035 (s), 849 (m), 768 (s). LC−MS (ESI) m/z = 402.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{20}H_{27}NO_4F_3$ 402.1892; found 402.1884 (Δ 2.0 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl 5-(2-methoxypyrimidine-5-yl)-4-methylpyrrolidine-2,4-dicarboxylate, (**11l**).* Yield: 90% (3.3 g; 9.0 mmol). Appearance: pale yellow wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.97 (s, 1H), 3.94 (s, 3H), 3.92−3.98 (m, 1H), 2.70 (br s, 1H), 2.59 (dd, J = 13.2, 8.2 Hz, 1H), 2.04 (dd, J = 13.2, 8.2 Hz, 1H), 1.39 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 172.8 (C), 165.3 (C), 158.3 (2CH), 127.0 (C), 81.4 (C), 67.9 (CH), 61.2 (CH_2), 58.6 (CH), 54.9 (C+CH_3), 40.6 (CH_2), 27.6 ($3CH_3$), 23.8 (CH_3), 14.2 (CH_3). IR (neat, cm^{-1}) 3350 (w), 2978 (w), 1742 (s), 1715 (s), 1596 (m), 1561 (m), 1475 (s), 1407 (s), 1320 (s), 1205 (s), 1156 (s), 1032 (s), 848 (m), 806 (m). LC−MS (ESI) m/z = 366.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{18}H_{28}N_3O_5$ 366.2029; found 366.2009 (Δ 5.5 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl 5-(4-bromo-3-iodophenyl)-4-methylpyrrolidine-2,4-dicarboxylate, (**11m**).* Yield: 81% (4.3 g; 8.1 mmol). Appearance: yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 2.1, 0.6 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.22 (ddd, J = 8.3, 2.1, 0.6 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.93−3.99 (m, 2H), 2.60 (dd, J = 13.2, 8.9 Hz, 1H), 2.34 (br s, 1H), 2.05 (dd, J = 13.2, 8.1 Hz, 1H), 1.42 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.13 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C), 172.9 (C), 141.3 (C), 139.2 (CH), 132.2 (CH), 128.5 (CH and C), 100.8 (C), 81.2 (C), 71.3 (CH), 61.2 (CH_2), 58.7 (CH), 55.0 (C), 41.2 (CH_2), 27.6 ($3CH_3$), 24.3 (CH_3), 14.3 (CH_3). IR (neat, cm^{-1}) 2977 (w), 1720 (s), 1450 (m), 1368 (m), 1248 (m), 1196 (m), 1151 (s), 1035 (m), 1009 (m), 847 (m). LC−MS (ESI) m/z = 538.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{19}H_{26}NO_4BrI$ 538.0090; found 538.0084 (Δ 1.1 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl 5-(4-bromophenyl)-4-methylpyrrolidine-2,4-dicarboxylate, (**11n**).* Yield: 93% (5.7 g; 14.0 mmol). Appearance: pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.98 (s, 1H), 3.95 (app t, J = 8.9 Hz, 1H), 2.78 (br s, 1H), 2.59 (dd, J = 13.1, 8.8 Hz, 1H), 2.04 (dd, J = 13.1, 8.1 Hz, 1H), 1.41 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C), 173.2 (C), 139.2 (C), 131.1 (2CH), 129.1 (2CH), 121.3 (C), 80.8 (C), 72.3 (CH), 61.1 (CH2), 58.8 (CH), 55.0 (C), 41.8 (CH_2), 27.5 ($3CH_3$), 24.3 (CH_3), 14.2 (CH_3). IR (neat, cm^{-1}) 2978 (w), 1720 (s), 1487 (w), 1448 (w), 1367 (m), 1248 (m), 1195 (s), 1150 (s), 1114 (m), 1010

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(s), 847 (m), 815 (m). LC−MS (ESI) m/z = 412.0 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{19}H_{27}NBrO_4$ 412.1123; found 412.1108 (Δ 3.6 ppm).

*Rac-(2S,4S,5S)-4-tert-Butyl 2-ethyl 5-(4-isobutylphenyl)-4-methylpyrrolidine-2,4-dicarboxylate, (**11o**).* Yield: 89% (5.2 g; 13.4 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.01 (s, 1H), 3.97 (app t, J = 8.8 Hz, 1H), 2.75 (br s, 1H), 2.60 (dd, J = 13.1, 8.8 Hz, 1H), 2.42 (d, J = 7.1 Hz, 2H), 2.07 (dd, J = 13.1, 8.1 Hz, 1H), 1.80 (dp, J = 13.5, 6.8 Hz, 1H), 1.45 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.05 (s, 9H), 0.86 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C), 173.6 (C), 140.9 (C), 137.1 (C), 128.8 (2CH), 127.0 (2CH), 80.5 (C), 72.9 (CH), 61.1 (CH_2), 59.0 (CH), 55.1 (C), 45.0 (CH_2), 42.4 (CH_2), 30.2 (CH), 27.5 ($3CH_3$), 24.3 (CH_3), 22.3 ($2CH_3$), 14.3 (CH_3). IR (neat, cm^{-1}) 2956 (w), 2870 (w), 1723 (s), 1449 (m), 1367 (M), 1248 (s), 1191 (s), 1151 (s), 1114 (s), 1034 (m), 848 (s), 794 (m). LC−MS (ESI) m/z = 390.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{23}H_{36}NO_4$ 390.2644; found 390.2645 (Δ 0.3 ppm).

General Experimental for Preparation of Compounds 4a−o. A solution of pyrrolidine **11** (1.0 equiv) in DCM (0.5 M) was prepared and placed in a water bath (room temperature) for the duration of the acylation reaction. To the mixture was added triethylamine (1.1 equiv) followed by slow addition of trimethylacetyl chloride (1.1 equiv) over several minutes. After 1.5 h stirring the resulting reaction mixture was quenched by addition of water and extracted three times with water (20 mL each time). The organic layer was dried over sodium sulfate, filtered and evaporated to dryness to give the desired acylation product typically as a yellow oil. This oil was redissolved in a mixture of THF, MeOH and water (3:5:2 by volume, 0.5 M total) and heated to 60 °C. A 3-fold excess of aqueous sodium hydroxide solution (6 M) was added and the reaction monitored by TLC or ^{1}H NMR for full consumption of the starting material. The reaction mixture was cooled to room temperature, acidified with hydrochloric acid (1 M aqueous) and extracted with DCM (three times 20 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated to give the desired acids **4** as waxy solids that in most cases can be recrystallized from solutions of DCM/toluene.

*Rac-(2S,4S,5R)-4-(Methoxycarbonyl)-4-methyl-1-pivaloyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylic acid, (**4a**).* Yield: 85% (3.0 g; 8.5 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (br s, 1H), 7.29 (dd, J = 3.7, 1.0 Hz, 1H), 7.21 (dd, J = 5.1, 1.2 Hz, 1H), 6.91 (dd, J = 5.1, 3.6 Hz, 1H), 5.42 (s, 1H), 4.67 (dd, J = 11.6, 7.6 Hz, 1H), 3.54 (s, 3H), 2.84 (dd, J = 13.3, 11.6 Hz, 1H), 2.06 (dd, J = 13.3, 7.5 Hz, 1H), 1.44 (s, 3H), 1.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1 (C), 174.3 (C), 171.9 (C), 141.3 (C), 127.5 (CH), 126.9 (CH), 125.6 (CH), 66.4 (CH), 60.5 (CH), 55.3 (C), 52.2 (CH_3), 39.8 (C), 31.6 (CH_2), 28.1 ($3CH_3$), 22.4 (CH_3). IR (neat, cm^{-1}) 2972 (w), 1733 (s), 1630 (m), 1403 (m), 1361 (m), 1243 (s), 1203 (s), 1129 (s), 909 (s), 727 (s), 647 (m). LC−MS (ESI) m/z = 354.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{17}H_{24}NO_5S$ 354.1375; found 354.1386 (Δ 3.1 ppm).

*Rac-(2S,4S,5S)-4-(Methoxycarbonyl)-4-methyl-1-pivaloyl-5-phenylpyrrolidine-2-carboxylic acid, (**4b**).* Yield: 85% (3.0 g; 8.5 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (br s, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.20−7.35 (m, 3H), 5.17 (s, 1H), 4.68 (dd, J = 12.0, 7.2 Hz, 1H), 3.32 (s, 3H), 2.81 (app t, J = 12.5 Hz, 1H), 2.01 (dd, J = 13.1, 7.3 Hz, 1H), 1.49 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3 (C), 175.2 (C), 171.9 (C), 139.0 (C), 128.3 (2CH), 128.0 (CH), 127.3 (2CH), 71.0 (CH), 61.2 (CH), 55.5 (C), 51.9 (CH_3), 39.7 (C), 31.7 (CH_2), 28.2 ($3CH_3$), 22.8 (CH_3). IR (neat, cm^{-1}) 2971 (w), 1731 (s), 1599 (s), 1455 (m), 1404 (s), 1359 (m), 1246 (s), 1202 (s), 1128 (s), 909 (m), 730 (s), 705 (s). LC−MS (ESI) m/z = 348.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{19}H_{26}NO_5$ 348.1811; found 348.1825 (Δ 4.0 ppm).

*Rac-(2S,4S,5S)-4-(Methoxycarbonyl)-4-methyl-1-pivaloyl-5-(o-tolyl)pyrrolidine-2-carboxylic acid, (**4c**).* Yield: 86% (3.1 g; 8.6 mmol). Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (br s, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.20 (t, J = 9.1 Hz, 1H), 7.13 (td, J = 7.4, 1.4 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 5.40 (s, 1H), 4.68 (dd, J = 12.0, 7.3 Hz, 1H), 3.17 (s, 3H), 3.01 (app t, J = 12.7 Hz, 1H), 2.34 (s, 3H), 1.99 (dd, J = 13.3, 7.3 Hz, 1H), 1.50 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3 (C), 175.4 (C), 171.9 (C), 138.0 (C), 133.9 (C), 130.6 (CH), 127.8 (CH), 127.5 (CH), 126.8 (CH), 67.5 (CH), 61.5 (CH), 55.3 (C), 51.9 (CH_3), 39.6 (C), 32.7 (CH_2), 27.9 ($3CH_3$), 22.9 (CH_3), 19.5 (CH_3). IR (neat, cm^{-1}) 2979 (w), 1721 (s), 1638 (s), 1352 (m), 1252 (s), 1206 (s), 1191 (s), 1174 (m), 932 (m), 902 (m), 744 (s), 674 (m). LC−MS (ESI) m/z = 362.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{20}H_{28}NO_5$ 362.1967; found 362.1969 (Δ 0.6 ppm). Melting range: 164.5−167.2 °C (toluene/DCM). Crystal data: CCDC 1504394, triclinic, space group $P\bar{1}$ (no. 2), a = 9.7331(7), b = 10.0362(7), c = 10.1379(7) Å, α = 84.043(3), β = 81.838(3), γ = 75.748(3)°, V = 947.7(1) Å^3, Z = 2, T = 120 K, R_1 = 4.8%.

*Rac-(2S,4S,5S)-5-(3-Bromo-4-chlorophenyl)-4-(methoxycarbonyl)-4-methyl-1-pivaloylpyrrolidine-2-carboxylic acid, (**4d**).* Yield: 85% (2.7 g; 6.0 mmol). Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (br s, 1H), 7.86 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 5.08 (s, 1H), 4.64 (dd, J = 12.0, 7.2 Hz, 1H), 3.44 (s, 3H), 2.64 (app t, J = 12.7 Hz, 1H), 2.04 (dd, J = 13.3, 7.2 Hz, 1H), 1.48 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6 (C), 175.7 (C), 171.6 (C), 139.8 (C), 134.1 (C), 132.6 (CH), 130.3 (CH), 127.5 (CH), 122.3 (C), 69.6 (CH), 60.9 (CH), 55.8 (C), 52.2 (CH_3), 39.6 (C), 31.9 (CH_2), 28.3 ($3CH_3$), 22.7 (CH_3). IR (neat, cm^{-1}) 2979 (w), 1743 (m), 1717 (s), 1644 (s), 1468 (m), 1402 (m), 1336 (s), 1261 (s), 1194 (s), 1128 (s), 1024 (m), 909 (m), 729 (s). LC−MS (ESI) m/z = 458.0 (M-H). HRMS (TOF-ES$^+$) calculated for $C_{19}H_{24}NO_5BrCl$ 460.0526; found 460.0522 (Δ 0.9 ppm).

*Rac-(2S,4S,5S)-4-(Methoxycarbonyl)-4-methyl-1-pivaloyl-5-(2-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylic acid, (**4e**).* Yield: 90% (3.7 g; 9.0 mmol). Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (br s, 1H), 8.34 (d, J = 8.2 Hz, 1H), 7.50−7.65 (m, 2H), 7.40 (t, J = 8.4 Hz, 1H), 5.64 (s, 1H), 4.67 (dd, J = 12.2, 7.2 Hz, 1H), 3.28 (s, 3H), 2.74 (app t, J = 12.6 Hz, 1H), 2.06 (dd, J = 13.0, 7.2 Hz, 1H), 1.46 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1 (C), 176.2 (C), 171.4 (C), 139.9 (C), 132.4 (CH), 129.3 (CH), 128.1 (CH), 126.8 (CH, q, J = 5 Hz), 126.5 (C, q, J = 30 Hz), 124.8 (CF_3, q, J = 276 Hz), 67.3 (CH), 61.3 (CH), 55.6 (C), 52.1 (CH_3), 39.5 (C), 34.8 (CH_2), 27.7 ($3CH_3$), 22.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.7. IR (neat, cm^{-1}) 2976 (w), 1736 (s), 1644 (s), 1307 (s), 1254 (m), 1202 (m), 1158 (s), 1129 (s), 1110 (s), 1037 (s), 907 (m), 768 (s), 661 (s). LC−MS (ESI) m/z = 416.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{20}H_{25}NO_5F_3$ 416.1685; found 416.1684 (Δ 0.2 ppm).

*Rac-(2S,4S,5S)-5-(5-Bromopyridin-3-yl)-4-4-(tert-butoxycarbonyl)-4-methyl-1-pivaloylpyrrolidine-2-carboxylic acid, (**4f**).* Yield: 84% (2.0 g; 4.2 mmol). Appearance: beige solid.

^{1}H NMR (400 MHz, DMSO) δ 12.83 (br s, 1H), 8.88 (br s, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.53 (br s, 1H), 5.21 (s, 1H), 4.43 (br s, 1H), 2.20−2.28 (m, 1H), 1.98−2.15 (m, 1H), 1.40 (s, 3H), 1.15 (s, 9H), 1.01 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 177.7 (C), 174.1 (C), 170.6 (C), 149.6 (CH), 148.5 (CH), 139.0 (C), 138.4 (CH), 120.2 (C), 81.6 (C), 67.3 (CH, broad), 60.7 (CH), 56.0 (C, broad), 33.0 (CH_2, broad), 28.4 ($3CH_3$), 27.7 ($3CH_3$), 23.1 (CH_3, broad); one resonance (C) not observed. IR (neat, cm^{-1}) 2974 (w), 1730 (m), 1705 (m), 1633 (s), 1355 (m), 1289 (m), 1217 (s), 1162 (s), 1131 (s), 842 (m), 751 (s), 713 (m), 666 (m), 648 (m). LC−MS (ESI) m/z = 469.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{21}H_{30}N_2O_5Br$ 469.1338; found 469.1330 (Δ 1.7 ppm).

*Rac-(2S,4S,5S)-5-(Benzo[d][1.3]dioxol-5-yl)-4-(tert-butoxycarbonyl)-4-methyl-1-pivaloylpyrrolidin-2-carboxylic acid, (**4g**).* Yield: 91% (3.9 g; 9.1 mmol). Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.4 (br s, 1H), 7.10 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.2, 1.8 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 5.93 (d, J = 1.4 Hz, 1H), 5.90 (d, J = 1.4 Hz, 1H), 5.03 (s, 1H), 4.61 (dd, J = 12.0, 7.2 Hz, 1H), 2.74 (app t, J = 12.7 Hz, 1H), 1.97 (dd, J = 13.3, 7.2 Hz, 1H), 1.42 (s, 3H), 1.21 (s, 9H), 1.12 (s, 9H). ^{13}C NMR (101

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MHz, $CDCl_3$) δ 180.1 (C), 175.6 (C), 170.7 (C), 147.4 (C), 147.0 (C), 133.0 (C), 121.8 (CH), 108.9 (CH), 108.0 (CH), 101.0 (CH_2), 81.6 (C), 70.5 (CH), 61.0 (CH), 55.9 (C), 39.6 (C), 32.0 (CH_2), 28.2 ($3CH_3$), 27.7 ($3CH_3$), 23.5 (CH_3). IR (neat, cm^{-1}) 2978 (w), 1718 (s), 1620 (s), 1489 (m), 1442 (m), 1292 (s), 1241 (s), 1164 (s), 1036 (s), 916 (s), 725 (s). LC−MS (ESI) m/z = 434.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{23}H_{32}NO_7$ 434.2179; found 434.2170 (Δ 2.1 ppm). Melting range: 170 °C (decomposition, toluene/DCM).

*Rac-(2S,4S,5S)-4-(tert-Butoxycarbonyl)-5-(3-fluorophenyl)-4-methyl-1-pivaloylpyrrolidine-2-carboxylic acid, (**4h**).* Yield: 90% (3.7 g; 9.0 mmol). Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (br s, 1H), 7.35−7.43 (m, 2H), 7.25−7.32 (m, 1H), 6.95 (dt, J = 1.9, 8.5 Hz, 1H), 5.10 (s, 1H), 4.64 (dd, J = 7.2, 12.0 Hz, 1H), 2.72 (app t, J = 12.6 Hz, 1H), 2.00 (dd, J = 7.2, 13.3 Hz, 1H), 1.45 (s, 3H), 1.17 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9 (C), 175.6 (C), 170.6 (C), 162.5 (CF, d, J = 247 Hz), 141.8 (C, d, J = 7 Hz), 129.8 (CH, d, J = 8 Hz), 123.9 (CH), 115.5 (CH, d, J = 23 Hz), 114.7 (CH, d, J = 21 Hz), 81.9 (C), 70.2 (CH), 61.0 (CH), 56.0 (C), 39.6 (C), 32.1 (CH_2), 28.2 ($3CH_3$), 27.6 ($3CH_3$), 23.6 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.6. IR (neat, cm^{-1}) 2977 (w), 1721 (m), 1615 (m), 1593 (m), 1369 (m), 1249 (m), 1163 (m), 1132 (m), 908 (m), 728 (s), 647 (m). LC−MS (ESI) m/z = 408.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{22}H_{31}NO_5F$ 408.2186; found 408.2177 (Δ 2.2 ppm). Melting range: > 170 °C (decomposition; toluene/DCM).

*Rac-(2S,4S,5S)-4-(tert-Butoxycarbonyl)-5-(3-methoxyphenyl)-4-methyl-1-pivaloylpyrrolidine-2-carboxylic acid, (**4i**).* Yield: 86% (3.6 g; 8.6 mmol). Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 7.14−7.30 (m, 2H), 6.99 (d, J = 8.2 Hz, 1H), 6.81 (dd, J = 8.2, 2.6 Hz, 1H), 5.13 (s, 1H), 4.67 (dd, J = 11.8, 7.3 Hz, 1H), 3.79 (s, 3H), 2.86 (app t, J = 13.2 Hz, 1H), 2.00 (dd, J = 13.4, 7.3 Hz, 1H), 1.46 (s, 3H), 1.18 (s, 9H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.7 (C), 175.2 (C), 170.6 (C), 159.7 (C), 140.4 (C), 129.2 (CH), 120.7 (CH), 114.4 (CH), 112.8 (CH), 81.7 (C), 70.8 (CH), 61.2 (CH), 55.7 (C), 55.4 (CH_3), 39.7 (C), 32.2 (CH_2), 28.2 ($3CH_3$), 27.6 ($3CH_3$), 23.7 (CH_3). IR (neat, cm^{-1}) 2974 (m), 1722 (s), 1603 (s), 1467 (m), 1368 (s), 1255 (s), 1210 (m), 1164 (s), 1132 (s), 1039 (m), 845 (m), 736 (m), 699 (m). LC−MS (ESI) m/z = 420.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{23}H_{34}NO_6$ 420.2386; found 420.2382 (Δ 1.0 ppm).

*Rac-(2S,4S,5R)-4-(tert-Butoxycarbonyl)-4-methyl-1-pivaloyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylic acid, (**4j**).* Yield: 91% (3.6 g; 9.1 mmol). Appearance: off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 5.1, 1.2 Hz, 1H), 7.12 (d, J = 3.6 Hz, 1H), 6.92 (dd, J = 5.1, 3.6 Hz, 1H), 5.42 (s, 1H), 4.69 (dd, J = 11.2, 7.8 Hz, 1H), 2.95 (dd, J = 13.7, 11.2 Hz, 1H), 2.01 (dd, J = 13.7, 7.8 Hz, 1H), 1.40 (s, 3H), 1.25 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1 (C), 173.0 (C), 170.9 (C), 141.1 (C), 127.6 (CH), 126.7 (CH), 125.5 (CH), 82.0 (C), 66.3 (CH), 60.9 (CH), 55.5 (C), 39.9 (C), 31.6 (CH_2), 28.1 ($3CH_3$), 27.7 ($3CH_3$), 23.5 (CH_3). IR (neat, cm^{-1}) 2982 (w), 1723 (s), 1574 (s), 1403 (s), 1365 (m), 1256 (s), 1229 (m), 1130 (s), 850 (m), 704 (s). LC−MS (ESI) m/z = 394.1 (M-H). HRMS (TOF-ES$^+$) calculated for $C_{20}H_{28}NO_5S$ 394.1688; found 394.1690 (Δ 0.5 ppm). Melting range: 140.5−143.1 °C (DCM).

*Rac-(2S,4S,5S)-4-(tert-Butoxycarbonyl)-4-methyl-1-pivaloyl-5-(2-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylic acid, (**4k**).* Yield: 85% (3.9 g; 8.5 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (br s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 5.55 (s, 1H), 4.64 (dd, J = 12.2, 7.2 Hz, 1H), 2.72 (app t, J = 12.6 Hz, 1H), 2.03 (dd, J = 12.9, 7.2 Hz, 1H), 1.40 (s, 3H), 1.03 (s, 9H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2 (C), 175.9 (C), 169.7 (C), 139.6 (C), 132.4 (CH), 129.6 (CH), 127.9 (CH), 127.0 (C, q, J = 30 Hz), 126.5 (CH, q, J = 3 Hz), 124.6 (CF_3, q, J = 275 Hz), 81.4 (C), 67.4 (CH), 61.3 (CH), 56.0 (C), 39.4 (C), 35.3 (CH_2), 27.6 ($3CH_3$), 27.2 ($3CH_3$), 22.4 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.9. IR (neat, cm^{-1}) 2979 (w), 1725 (m), 1629 (m), 1368 (m), 1307 (s), 1161 (s), 1114 (s), 1037 (m), 909 (s), 774 (m), 729 (s), 661 (m), 647 (m). LC−MS (ESI) m/z = 458.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{23}H_{31}NO_5F_3$ 458.2154; found 458.2146 (Δ 1.7 ppm).

*Rac-(2S,4S,5S)-4-(tert-Butoxycarbonyl)- 5-(2-methoxypyrimidin-5-yl)-4-methyl-1-pivaloylpyrrolidine-2-carboxylic acid, (**4l**).* Yield: 88% (3.7 g; 8.8 mmol). Appearance: off-white solid.

^{1}H NMR (400 MHz, MeOD/$CDCl_3$) δ 8.90 (s, 2H), 5.11 (s, 1H), 4.59 (br s, 1H), 4.00 (s, 3H), 2.49 (br s, 1H), 2.16 (dd, J = 13.2, 7.1 Hz, 1H), 1.48 (s, 3H), 1.24 (s, 9H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, MeOD/$CDCl_3$) δ 179.1 (C), 173.9 (C), 171.0 (C), 164.8 (C), 159.5 (2CH), 127.1 (C), 82.5 (C), 60.7 (CH), 54.8 (CH_3), 39.5 (C), 27.9 ($3CH_3$), 27.2 ($3CH_3$), 22.9 (CH_3) [3 resonances not observed]. IR (neat, cm^{-1}) 2977 (w), 1726 (s), 1644 (s), 1603 (m), 1578 (m), 1490 (s), 1413 (s), 1338 (s), 1250 (s), 1201 (m), 1126 (s), 1097 (m), 1036 (m), 972 (m), 836 (m), 665 (s), 632 (m). LC−MS (ESI) m/z = 422.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{21}H_{32}N_3O_6$ 422.2291; found 422.2303 (Δ 2.8 ppm).

*Rac-(2S,4S,5S)-4-(tert-Butoxycarbonyl)-5-(4-bromo-3-iodophenyl)-4-methyl-1-pivaloylpyrrolidine-2-carboxylic acid, (**4m**).* Yield: 87% (5.2 g; 8.7 mmol). Appearance: beige solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 8.04 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 4.96 (s, 1H), 4.56 (m, 1H), 2.57 (app t, J = 12.7 Hz, 1H), 1.98 (m, 1H), 1.41 (s, 3H), 1.18 (s, 9H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5 (C), 176.1 (C), 170.5 (C), 140.3 (C), 140.1 (CH), 132.5 (CH), 129.4 (CH), 129.2 (C), 100.9 (C), 82.3 (C), 69.2 (CH), 61.0 (CH), 56.1 (C), 39.6 (C), 32.2 (CH_2), 28.3 ($3CH_3$), 27.8 ($3CH_3$), 23.6 (CH_3). IR (neat, cm^{-1}) 2972 (w), 1721 (s), 1634 (m), 1454 (m), 1404 (m), 1367 (s), 1329 (m), 1290 (m), 1252 (s), 1201 (s), 1166 (s), 1129 (s), 1099 (m), 1009 (m), 844 (m), 822 (m), 757 (m). LC−MS (ESI) m/z = 594.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{22}H_{30}NO_5BrI$ 594.0352; found 594.0350 (Δ 0.3 ppm).

*Rac-(2S,4S,5S)-4-(tert-Butoxycarbonyl)-5-(4-bromophenyl)-4-methyl-1-pivaloylpyrrolidin-2-carboxylic acid, (**4n**).* Yield: 89% (3.2 g; 7.1 mmol). Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.10 (s, 1H), 4.69 (dd, J = 11.6, 7.5 Hz, 1H), 2.82 (dd, J = 13.3, 12.0 Hz, 1H), 1.97 (dd, J = 13.7, 7.4 Hz, 1H), 1.43 (s, 3H), 1.17 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3 (C), 173.5 (C), 170.6 (C), 137.7 (C), 131.5 (2CH), 129.8 (2CH), 122.1 (C), 82.1 (C), 70.3 (CH), 61.2 (CH), 55.4 (C), 39.8 (C), 31.7 (CH_2), 28.3 ($3CH_3$), 27.7 ($3CH_3$), 23.9 (CH_3). IR (neat, cm^{-1}) 2979 (m), 1749 (s), 1726 (s), 1592 (s), 1487 (m), 1408 (m), 1366 (s), 1249 (s), 1160 (s), 1126 (s), 1096 (s), 842 (m), 809 (m), 756 (m), 659 (m), 529 (m). LC−MS (ESI) m/z = 468.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{22}H_{31}NO_5Br$ 468.1386; found 468.1396 (Δ 2.1 ppm). Melting range: 170.0−172.8 °C (toluene, DCM).

*Rac-(2S,4S,5S)-4-(tert-Butoxycarbonyl)-5-(4-isobutylphenyl)-4-methyl-1-pivaloylpyrrolidin-2-carboxylic acid, (**4o**).* Yield: 92% (4.1 g; 9.2 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 5.14 (s, 1H), 4.73 (dd, J = 11.3, 7.7 Hz, 1H), 2.98 (dd, J = 13.8, 11.3 Hz, 1H), 2.42 (d, J = 7.2 Hz, 2H), 1.96 (dd, J = 13.6, 7.7 Hz, 1H), 1.80 (heptet, J = 6.8 Hz, 1H), 1.42 (s, 3H), 1.15 (s, 9H), 1.14 (s, 9H), 0.86 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.1 (C), 172.6 (C), 170.8 (C), 141.5 (C), 135.4 (C), 129.1 (2CH), 127.7 (2CH), 81.6 (C), 70.8 (CH), 61.5 (CH), 54.9 (C), 45.0 (CH_2), 39.9 (C), 31.5 (CH_2), 30.1 (CH), 28.3 ($3CH_3$), 27.7 ($3CH_3$), 24.1 (CH_3), 22.3 (CH_3), 22.2 (CH_3). IR (neat, cm^{-1}) 2961 (m), 1715 (s), 1628 (s), 1464 (m), 1366 (s), 1353 (m), 1293 (m), 1216 (s), 1163 (s), 1129 (s), 921 (m), 846 (m), 758 (m), 680 (m), 550 (m). LC−MS (ESI) m/z = 446.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{26}H_{40}NO_5$ 446.2906; found 446.2905 (Δ 0.2 ppm).

General Procedure for Preparation of Compounds 12a−o and 17h. To a stirred solution of acid **4** (1.0 equiv., 0.3 M toluene) was added pyridine (2 mL per mmol of **4**), DMAP (10 mol %) and trifluoroacetic anhydride (3.0 equiv). After stirring the resulting solution at room temperature for 1 h, the temperature was increased to 90 °C and maintained for 2 h. The reaction mixture was subsequently cooled to about 60 °C and quenched with a mixture of water and methanol (1:1; ∼25 mL). The crude product was partitioned between

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ethyl acetate and water and extracted three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Final purification was accomplished by silica column chromatography (10−20% ethyl acetate/hexanes) to yield the desired products **12** typically as colorless oils after removal of the solvents.

In order to isolate compound **17h** (and its derivatives) hexanes (20 mL) is added to the crude reaction mixture (no quenching) after removal of all volatiles. The resulting suspension is filtered and the solid material is washed with hexanes (20 mL). The combined filtrates are evaporated and analyzed by NMR. Careful flash column chromatography can be used on deactivated silica gel in order to further purify this material (eluent 10% ethyl acetate/hexanes).

*Rac-(2R,3S,5S)-Methyl 3-methyl-1-pivaloyl-2-(thiophen-2-yl)-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12a**).* Yield: 85% (689 mg; 1.7 mmol). Appearance: colorless oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42 (d, J = 3.6 Hz, 1H), 7.22 (dd, J = 1.2, 5.2 Hz, 1H), 6.93 (dd, J = 3.6, 5.2 Hz, 1H), 5.37 (s, 1H), 4.92 (dd, J = 6.8, 12.6 Hz, 1H), 3.50 (s, 3H), 2.62 (app t, J = 12.6, 1H), 2.08 (dd, J = 6.8, 12.6 Hz, 1H), 1.50 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 187.6 (q, J = 34 Hz, C), 177.8 (C), 171.3 (C), 141.5 (C), 127.5 (CH), 126.8 (CH), 125.8 (CH), 115.8 (q, J = 293 Hz, CF_3), 65.9 (CH), 60.7 (CH), 56.8 (C), 52.2 (CH_3), 39.2 (C), 31.6 (CH_2), 27.8 ($3CH_3$), 22.2 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.1. IR (neat, cm^{-1}) 2971 (w), 1739 (s), 1608 (m), 1347 (m), 1280 (m), 1204 (s), 1150 (s), 1039 (s), 910 (s), 855 (m), 725 (s), 703 (s). LC−MS (ESI) m/z = 406.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{18}H_{23}NSO_4F_3$ 406.1300; found 406.1288 (Δ 3.0 ppm).

*Rac-(2S,3S,5S)-Methyl 3-methyl-2-phenyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12b**).* Yield: 78% (622 mg; 1.6 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.25−7.40 (m, 3H), 5.14 (s, 1H), 4.99 (dd, J = 6.6, 12.4 Hz, 1H), 3.33 (s, 3H), 2.66 (app t, J = 12.4 Hz, 1H), 2.04 (dd, J = 6.6, 12.4 Hz, 1H), 1.59 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.1 (q, J = 34 Hz, C), 178.2 (C), 171.4 (C), 139.1 (C), 128.3 (2CH), 128.4 (CH), 127.4 (2CH), 116.0 (q, J = 290 Hz, CF_3), 70.3 (CH), 60.9 (CH), 57.0 (C), 52.0 (CH_3), 39.1 (C), 31.8 (CH_2), 28.0 ($3CH_3$), 22.9 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2973 (w), 1736 (s), 1602 (m), 1456 (m), 1299 (m), 1203 (s), 1142 (s), 1055 (m), 918 (m), 725 (s), 705 (s). LC−MS (ESI) m/z = 400.2 (M+H). HRMS(TOF-ES$^+$) calculated for $C_{20}H_{25}NO_4F_3$ 400.1736; found 400.1727 (Δ −2.2 ppm).

*Rac-(2S,3S,5S)-Methyl 3-methyl-1-pivaloyl-2-(o-tolyl)-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12c**).* Yield: 76% (471 mg; 1.1 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 1.4, 7.9 Hz, 1H), 7.28 (dt, J = 1.4, 7.4 Hz, 1H), 7.19 (ddd, J = 1.4, 6.1, 7.4 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 5.39 (s, 1H), 4.98 (dd, J = 6.6, 12.4 Hz, 1H), 3.20 (s, 3H), 2.84 (app. t, J = 12.7 Hz, 1H), 2.39 (s, 3H), 2.00 (dd, J = 6.6, 13.0 Hz, 1H), 1.61 (s, 3H), 1.05 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.7 (q, J = 34 Hz, C), 178.2 (C), 171.3 (C), 138.0 (C), 134.1 (C), 130.7 (CH), 128.1 (CH), 127.3 (CH), 126.4 (CH), 116.0 (q, J = 293 Hz, CF_3), 66.6 (CH), 61.0 (CH), 57.0 (C), 52.0 (CH_3), 39.0 (C), 32.5 (CH_2), 27.7 ($3CH_3$), 23.2 (CH_3), 19.4 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2973 (w), 1734 (s), 1605 (m), 1465 (m), 1351 (m), 1297 (s), 1207 (s), 1137 (s), 1043 (s), 906 (m), 755 (m), 727 (m). LC−MS (ESI) m/z = 414.1 (M +H). HRMS (TOF-ES$^+$) calculated for $C_{21}H_{27}NO_4F_3$ 414.1892; found 414.1895 (Δ 0.7 ppm).

*Rac-(2R,3S,5S)-Methyl 2-(3-bromo-4-chlorophenyl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12d**).* Yield: 70% (358 mg; 0.7 mmol). Appearance: colorless oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.85 (br s, 1H), 7.66 (br s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 5.07 (s, 1H), 4.94 (dd, J = 12.3, 6.7 Hz, 1H), 3.46 (s, 3H), 2.50 (app t, J = 12.7 Hz, 1H), 2.04 (dd, J = 13.1, 6.7 Hz, 1H), 1.56 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.5 (C, q, J = 35 Hz), 177.9 (C), 171.0 (C), 139.6 (C), 134.5 (C), 132.5 (CH), 130.4 (CH), 127.3 (CH), 122.5 (C), 115.8 (CF_3, q, J = 292 Hz), 68.8 (CH), 60.8 (CH), 57.1 (C), 52.3 (CH_3), 39.1 (C), 31.8 (CH_2), 28.1 ($3CH_3$), 22.8 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2972 (w), 1737 (m), 1625 (m), 1468 (m), 1402 (m), 1345 (m), 1300 (m), 1208 (s), 1151 (m), 1057 (m), 1024 (m), 727 (m). LC−MS (ESI) m/z = 512.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{20}H_{23}NO_4F_3ClBr$ 512.0451; found 512.0455 (Δ 0.8 ppm).

*Rac-(2S,3S,5S)-Methyl 3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)-2-(2-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylate, (**12e**).* Yield: 81% (378 mg; 0.8 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 7.62−7.70 (m, 2H), 7.47 (t, J = 8.0 Hz, 1H), 5.68 (s, 1H), 5.00 (dd, J = 6.6, 12.6 Hz, 1H), 3.32 (s, 3H), 2.66 (app t, J = 12.6 Hz, 1H), 2.08 (dd, J = 6.6, 12.8 Hz, 1H), 1.58 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 188.2 (C, q, J = 34 Hz), 178.4 (C), 170.8 (C), 138.6 (C), 132.5 (CH), 128.9 (CH), 128.4 (CH), 127.0 (CH, q, J = 5 Hz), 126.6 (C, q, J = 30 Hz), 124.7 (CF_3, q, J = 273 Hz), 115.9 (CF_3, q, J = 291 Hz), 66.3 (CH), 61.1 (CH), 57.0 (C), 52.2 (CH_3), 38.9 (C), 34.2 (CH_2), 27.5 ($3CH_3$), 22.2 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.6, −77.2. IR (neat, cm^{-1}) 2978 (w), 1736 (m), 1610 (w), 1307 (s), 1204 (s), 1156 (s), 1114 (s), 1036 (s), 908 (m), 774 (m), 725 (m). LC−MS (ESI) m/z = 468.2 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{21}H_{24}NO_4F_6$ 468.1610; found 468.1617 (Δ 1.5 ppm).

*Rac-(2S,3S,5S)-Methyl 3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)-2-(2-(trifluoromethyl)-phenyl)pyrrolidine-3-carboxylate, (**12f**).* Yield: 70% (728 mg; 1.4 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 2.1 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.42 (t, J = 2.1 Hz, 1H), 5.06 (s, 1H), 4.92 (dd, J = 12.1, 6.6 Hz, 1H), 2.44 (app t, J = 12.7 Hz, 1H), 2.05 (dd, J = 13.2, 6.6 Hz, 1H), 1.54 (s, 3H), 1.19 (s, 9H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.7 (C, q, J = 35 Hz), 177.8 (C), 169.7 (C), 150.5 (CH), 147.9 (CH), 137.9 (CH), 137.0 (C), 120.8 (C), 115.9 (CF_3, q, J = 292 Hz), 82.9 (C), 67.0 (CH), 60.7 (CH), 57.5 (C), 39.1 (C), 32.2 (CH_2), 28.1 ($3CH_3$), 27.6 ($3CH_3$), 23.7 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2978 (w), 1727 (s), 1608 (m), 1348 (m), 1299 (m), 1206 (s), 1162 (s), 1130 (s), 1104 (s), 1051 (m), 920 (m), 847 (m), 728 (s). LC−MS (ESI) m/z = 521.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{22}H_{29}N_2O_4BrF_3$ 521.1263; found 521.1248 (Δ 2.9 ppm).

*Rac-(2S,3S,5S)-tert-Butyl 2-(benzo[d][1,3]dioxol-5-yl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12g**).* Yield: 84% (2.0 g; 4.2 mmol). Appearance: colorless solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.15 (br s, 1H), 7.11 (br d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1 H), 4.96 (s, 1H), 4.86 (dd, J = 6.6, 12.3 Hz, 1H), 2.53 (app t, J = 13.0 Hz, 1H), 1.96 (dd, J = 6.4, 13.0 Hz, 1H), 1.48 (s, 3H), 1.19 (s, 9H), 1.04 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.2 (q, J = 34 Hz, C), 178.0 (C), 170.1 (C), 147.5 (C), 147.3 (C), 134.0 (CH), 121.8 (C), 115.9 (q, J = 293 Hz, CF_3), 108.8 (CH), 108.0 (CH), 101.1 (CH_2), 81.8 (C), 67.8 (CH), 60.6 (CH), 57.4 (C), 39.0 (C), 32.1 (CH_2), 27.9 ($3CH_3$), 27.6 ($3CH_3$), 23.6 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2972 (w), 2930 (w), 1725 (m), 1612 (m), 1491 (s), 1447 (m), 1369 (s), 1298 (m), 1239 (s), 1208 (s), 1130 (s), 1038 (s), 925 (m), 845 (m), 724 (s). LC−MS (ESI) m/z = 486.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{24}H_{31}NO_6F_3$ 486.2103; found 486.2110 (Δ 1.4 ppm). Melting range (MeOH/DCM): 120.1−123.0 °C. Crystal data: CCDC 1504395, orthorhombic, space group *Pbca* (no. 61), a = 19.8948(9), b = 9.9946(5), c = 23.9226(11) Å, V = 4756.8(4) Å^3, Z = 8, T = 120 K, R_1 = 4.5%.

*Rac-(2S,3S,5S)-tert-Butyl 2-(3-fluorophenyl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12h**).* Yield: 83% (1.9 g; 4.2 mmol). Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.30 (td, J = 8.0, 5.9 Hz, 1H), 6.97 (tdd, J = 8.3, 2.6, 1.0 Hz, 1H), 5.05 (s, 1H), 4.91 (dd, J = 12.2, 6.6 Hz, 1H), 2.53 (app t, J = 12.5 Hz, 1H), 2.01 (dd, J = 13.0, 6.6 Hz, 1H), 1.52 (s, 3H), 1.16 (s, 9H), 1.03 (s, 9H) . ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3 (C, q, J = 34 Hz), 177.9 (C), 169.9 (C), 162.5 (CF, d, J = 248 Hz), 141.8 (C, d, J = 7 Hz), 130.0 (CH, d, J = 8 Hz), 123.9 (CH, d, J = 3 Hz), 115.9 (CF_3, q, J = 293 Hz), 115.4 (CH, d, J = 23 Hz), 115.1 (CH, d, J = 21 Hz), 82.1 (C), 69.5 (CH), 60.7 (CH), 57.4 (C), 39.0 (C), 32.1 (CH_2), 27.9

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($3CH_3$), 27.5 ($3CH_3$), 23.7 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2, −112.3. IR (neat, cm^{-1}) 2977 (w), 1724 (m), 1614 (m), 1454 (w), 1370 (m), 1347 (m), 1298 (m), 1207 (s), 1146 (s), 1053 (m), 912 (s), 844 (m), 730 (s). LC−MS (ESI) m/z = 460.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{23}H_{30}NO_4F_4$ 460.2111; found 460.2098 (Δ 2.8 ppm).

*Rac-(2S,3S,5S)-tert-Butyl 2-(3-methoxyphenyl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12i**).* Yield: 72% (678 mg; 1.4 mmol). Appearance: colorless oil.

^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (br s, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.09 (br d, J = 7.8 Hz, 1H), 6.80 (ddd, J = 0.9, 2.5, 7.8 Hz, 1H), 5.02 (s, 1H), 4.89 (dd, J = 6.6, 12.3 Hz, 1H), 3.82 (s, 3H), 2.58 (app t, J = 12.6 Hz, 1H), 1.97 (dd, J = 6.6, 13.0 Hz, 1H), 1.50 (s, 3H), 1.13 (s, 9H), 1.02 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.3 (q, J = 34 Hz, C), 178.0 (C), 170.0 (C), 159.7 (C), 140.6 (CH), 129.2 (CH), 120.8 (CH), 115.9 (q, J = 293 Hz, CF_3), 114.4 (CH), 112.9 (C), 81.8 (C), 70.0 (CH), 60.6 (CH), 57.8 (C), 55.5 (CH_3), 39.0 (C), 32.3 (CH_2), 27.9 ($3CH_3$), 27.5 ($3CH_3$), 23.8 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2971 (w), 1725 (s), 1603 (s), 1467 (m), 1369 (m), 1348 (m), 1298 (s), 1255 (s), 1208 (s), 1134 (s), 1041 (s), 913 (s), 844 (s), 725 (s). LC−MS (ESI) m/z = 472.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{24}H_{33}NO_5F_3$ 472.2311; found 472.2299 (Δ −2.5 ppm).

*Rac-(2R,3S,5S)-tert-Butyl 3-methyl-1-pivaloyl-2-(thiophen-2-yl)-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12j**).* Yield: 91% (814 mg; 1.8 mmol). Appearance: colorless oil.

^1H NMR (700 MHz, $CDCl_3$) δ 7.31 (d, J = 3.6 Hz, 1H), 7.23 (dd, J = 1.2, 5.1 Hz, 1H), 6.93 (dd, J = 3.6, 5.1 Hz, 1H), 5.33 (s, 1H), 4.89 (dd, J = 6.8, 12.1 Hz, 1H), 2.62 (app. t, J = 12.6 Hz, 1H), 2.05 (dd, J = 6.8, 13.1 Hz, 1H), 1.47 (s, 3H), 1.20 (s, 9H), 1.07 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 187.5 (q, J = 34 Hz, C), 177.7 (C), 170.2 (C), 141.7 (C), 127.9 (CH), 126.5 (CH), 125.7 (CH), 115.9 (q, J = 292 Hz, CF_3), 82.1 (C), 65.8 (CH), 60.7 (CH), 57.3 (C), 39.1 (C), 31.9 (CH_2), 27.7 ($3CH_3$), 27.6 ($3CH_3$), 23.1 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.1. IR (neat, cm^{-1}) 2977 (w), 1775 (w), 1725 (m), 1616 (m), 1298 (m), 1207 (s), 1150 (s), 1039 (s), 910 (s), 844 (m), 729 (s), 703 (s). LC−MS (ESI) m/z = 448.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{21}H_{29}NO_4SF_3$ 448.1769; found 448.1776 (Δ 1.6 ppm).

*Rac-(2S,3S,5S)-tert-Butyl 3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)-2-(2-(trifluoromethyl)phenyl)-pyrrolidine-3-carboxylate, (**12k**).* Yield: 77% (588 mg; 1.2 mmol). Appearance: colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 8.0 Hz, 1H), 7.63−7.70 (m, 2H), 7.48 (t, J = 8.0 Hz, 1H), 5.57 (s, 1H), 4.96 (dd, J = 12.5, 6.6 Hz, 1H), 2.61 (app t, J = 12.5 Hz, 1H), 2.05 (dd, J = 12.5, 6.6 Hz, 1H), 1.52 (s, 3H), 1.06 (s, 9H), 1.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4 (C, q, J = 34 Hz), 178.5 (C), 169.1 (C), 139.4 (C), 132.5 (CH), 129.3 (CH), 128.2 (CH), 127.1 (C, q, J = 28.0 Hz), 126.7 (CH, q, J = 6 Hz), 124.5 (CF_3, q, J = 275 Hz), 115.9 (CF_3, q, J = 293 Hz), 81.7 (C), 66.5 (CH), 61.1 (CH), 57.5 (C), 38.9 (C), 34.9 (CH_2), 27.4 ($3CH_3$), 27.2 ($3CH_3$), 22.6 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.7, −77.1. IR (neat, cm^{-1}) 2981 (w), 1729 (m), 1623 (w), 1456 (w), 1369 (w), 1308 (s), 1209 (s), 1160 (s), 1116 (s), 1037 (s), 847 (m), 773 (m), 724 (m). LC−MS (ESI) m/z = 510.0 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{24}H_{30}NO_4F_6$ 510.2079; found 510.2087 (Δ 1.6 ppm).

*Rac-(2S,3S,5S)-tert-Butyl 2-(2-methoxypyrimidin-5-yl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)-pyrrolidine-3-carboxylate, (**12l**).* Yield: 85% (804 mg; 1.7 mmol). Appearance: off-white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 2H), 5.00 (s, 1H), 4.89 (dd, J = 6.7, 12.1 Hz, 1H), 3.97 (s, 3H), 2.37 (app t, J = 12.7 Hz, 1H), 2.06 (dd, J = 6.7, 13.3 Hz, 1H), 1.49 (s, 3H), 1.18 (s, 9H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4 (C, q, J = 34 Hz), 177.7 (C), 170.0 (C), 165.4 (C), 159.1 (2CH), 126.3 (C), 115.8 (CF_3, q, J = 293 Hz), 82.9 (C), 65.5 (CH), 60.7 (CH), 57.4 (C), 55.1 (CH_3), 39.1 (C), 31.9 (CH_2), 28.1 ($3CH_3$), 27.6 ($3CH_3$), 23.4 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2977 (m), 1724 (m), 1598 (s), 1559 (m), 1475 (s), 1410 (s), 1325 (s), 1299 (m), 1207 (s), 1159 (s), 1033 (m), 917 (m), 843 (m), 725 (m). LC−MS (ESI) m/z = 474.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{22}H_{31}N_3O_5F_3$ 474.2216; found 474.2198 (Δ 3.8 ppm).

*Rac-(2R,3S,5S)-tert-Butyl 2-(4-bromo-3-iodophenyl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)-pyrrolidine-3-carboxylate, (**12m**).* Yield: 79% (1170 mg; 2.4 mmol). Appearance: yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.68 (br d, J = 8.3 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 4.94 (s, 1H), 4.88 (dd, J = 12.2, 6.6 Hz, 1H), 2.44 (app t, J = 12.7 Hz, 1H), 1.99 (dd, J = 13.1, 6.6 Hz, 1H), 1.49 (s, 3H), 1.19 (s, 9H), 1.02 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.5 (C, q, J = 34 Hz), 177.9 (C), 169.9 (C), 140.2 (C), 140.0 (CH), 132.6 (CH), 129.6 (C), 129.0 (CH), 115.9 (CF_3, q, J = 293 Hz), 101.0 (C), 82.6 (C), 68.5 (CH), 60.7 (CH), 57.4 (C), 39.1 (C), 32.2 (CH_2), 28.1 ($3CH_3$), 27.7 ($3CH_3$), 23.8 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2976 (w), 1776 (m), 1723 (m), 1617 (m), 1454 (m), 1345 (s), 1298 (s), 1208 (s), 1148 (s), 1054 (m), 910 (s), 727 (s). LC−MS (ESI) m/z = 646.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{23}H_{29}NO_4F_3BrI$ 646.0277; found 646.0271 (Δ 0.9 ppm).

*Rac-(2S,3S,5S)-tert-Butyl 2-(4-bromophenyl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12n**).* Yield: 89% (924 mg; 1.8 mmol). Appearance: colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.99 (s, 1H), 4.88 (dd, J = 6.6, 12.3 Hz, 1H), 2.48 (app. t, J = 12.7 Hz, 1H), 1.98 (dd, J = 6.6, 13.0 Hz, 1H), 1.49 (s, 3H), 1.12 (s, 9H), 1.00 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4 (q, J = 34 Hz, C), 178.0 (C), 170.0 (C), 138.3 (C), 131.4 (2CH), 130.1 (2CH), 122.3 (C), 115.9 (q, J = 293 Hz, CF_3), 82.2 (C), 69.5 (CH), 60.7 (CH), 57.4 (C), 39.0 (C), 32.1 (CH_2), 27.9 ($3CH_3$), 27.5 ($3CH_3$), 23.8 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2973 (m), 1724 (m), 1606 (m), 1481 (m), 1370 (m), 1294 (m), 1210 (m), 1130 (s), 1012 (m), 951 (m), 845 (m), 813 (m), 725 (m). LC−MS (ESI) m/z = 420.1 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{23}H_{30}NO_4BrF_3$ 520.1310; found 520.1315 (Δ 1.0 ppm).

*Rac-(2S,3S,5S)-tert-Butyl 2-(4-isobutylphenyl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate, (**12o**).* Yield: 72% (716 mg; 1.4 mmol). Appearance: colorless oil.

^1H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 5.01 (s, 1H), 4.89 (dd, J = 6.6, 12.3 Hz, 1H), 2.59 (app t, J = 12.6 Hz, 1H), 2.43 (d, J = 7.0 Hz, 2H), 1.97 (dd, J = 6.6, 13.0 Hz, 1H), 1.79 (sept, J = 7.0 Hz, 1H), 1.50 (s, 3H), 1.10 (s, 9 H), 1.05 (s, 9 H), 0.85 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.1 (q, J = 34 Hz, C), 178.0 (C), 170.3 (C), 141.7 (C), 136.3 (C), 129.0 (2CH), 128.2 (2CH), 116.0 (q, J = 293 Hz, CF_3), 81.7 (C), 70.0 (CH), 60.7 (CH), 57.3 (C), 45.0 (CH_2), 39.0 (C), 32.2 (CH_2), 30.1 (CH), 27.8 ($3CH_3$), 27.5 ($3CH_3$), 23.8 (CH_3), 22.2 (CH_3), 22.1 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.2. IR (neat, cm^{-1}) 2960 (m), 2874 (w), 1726 (s), 1615 (m), 1368 (s), 1299 (s), 1208 (s), 1133 (s), 1042 (s), 917 (m), 846 (s), 724 (s). LC−MS (ESI) m/z = 498.3 (M+H). HRMS (TOF-ES$^+$) calculated for $C_{27}H_{39}NO_4F_3$ 498.2831; found 498.2838 (Δ 1.4 ppm).

*Rac-(6S)-5-(Benzo[d][1,3]dioxol-5-yl)-6-(tert-butoxycarbonyl)-3-(tert-butyl)-6-methyl-1-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo-[1,2-c]oxazol-4-ium 2,2,2-trifluoroacetate, (**5g**).* Yield: 10% (100 mg; 0.17 mmol). Appearance: colorless oil.

Major Diastereomer. ^1H NMR (700 MHz, $CDCl_3$) δ 6.80−6.82 (m, 2H), 6.73 (d, J = 8.6 Hz, 1H), 6.23 (s, 1H), 5.95 (d, J = 1.5 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 3.09 (dq, J = 1.6, 14.7 Hz, 1H), 2.86 (d, J = 14.7 Hz, 1H), 1.33−1.36 (m, 18 H), 1.22 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.9 (C), 170.9 (C), 156.0 (q, J = 44 Hz, C), 147.9 (C), 147.5 (C), 137.8 (q, J = 2 Hz, C), 135.2 (q, J = 42 Hz, C), 128.5 (C), 121.7 (CH), 119.7 (q, J = 267 Hz, CF_3), 114.53 (q, J = 286 Hz, CF_3), 108.0 (CH), 107.9 (CH), 101.2 (CH_2), 82.1 (C), 81.5 (CH), 51.4 (C), 34.9 (C), 31.9 (CH_2), 28.3 ($3CH_3$), 27.8 ($3CH_3$), 17.5 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.3 (s), −75.3 (s).

Minor Diastereomer. ^1H NMR (700 MHz, $CDCl_3$) δ 6.99 (d, J = 1.8 Hz, 1H), 6.97 (dd, J = 1.8, 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.54 (s, 1H), 5.97 (d, J = 1.5 Hz, 1H), 5.96 (d, J = 1.5 Hz, 1H), 2.73 (dq, J = 1.5, 14.7 Hz, 1H), 2.68 (d, J = 14.7 Hz, 1H), 1.39 (s, 9 H), 1.34 (s, 9H), 1.25 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.8 (C), 171.4 (C), 155.9 (q, J = 44 Hz, C), 148.1 (C), 147.6 (C), 137.3 (q, J = 2 Hz, C), 135.3 (q, J = 42 Hz, C), 128.2 (C), 122.1 (CH), 119.5 (q, J = 268 Hz, CF_3), 114.49 (q, J = 286 Hz, CF_3), 108.4 (CH), 107.9

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(CH), 101.3 (CH_2), 81.8 (C), 81.5 (CH), 50.7 (C), 34.0 (C), 32.1 (CH_2), 28.3 ($3CH_3$), 27.6 ($3CH_3$), 17.1 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.2 (s), −75.1 (s). IR (neat, cm^{-1}, mixture of diastereomers) ν/cm^{-1} 2979 (w), 1791 m), 1720 (w), 1492 (m), 1369 (m), 1221 (m), 1133 (s), 1107 (s), 1040 (s), 910 (s), 729 (s). LC−MS (ESI) m/z = 468.2 (cation M^+). HRMS (TOF-ES$^+$) calculated for $C_{24}H_{29}NO_5F_3$ 468.1998; found 468.1995 (Δ −0.6 ppm).

*Rac-(2S,3S,Z)-tert-Butyl 2-(3-fluorophenyl)-3-methyl-1-pivaloyl-5-(2,2,2-trifluoro-1-(2,2,2-trifluoro-acetoxy)ethylidene)pyrrolidine-3-carboxylate, (**17h**).* Yield: ∼80% (1350 mg; 2.4 mmol). Appearance: yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (td, J = 8.0, 5.8 Hz, 1H), 6.97−7.05 (m, 2H), 6.94 (dt, J = 9.7, 2.2 Hz, 1H), 5.15 (s, 1H), 3.44 (d, J = 17.4 Hz, 1H), 2.73 (dq, J = 17.6, 2.5 Hz, 1H), 1.45 (s, 3H), 1.25 (s, 9H), 1.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5 (C), 170.0 (C), 162.6 (CF, d, J = 249 Hz), 154.9 (C, q, J = 44 Hz), 139.5 (C, d, J = 7 Hz), 139.1 (C), 130.5 (CH, d, J = 9 Hz), 122.6 (CH, d, J = 2 Hz), 120.9 (CF_3, q, J = 274 Hz), 120.5 (C, q, J = 40 Hz), 115.5 (CH, d, J = 20 Hz), 114.8 (CH, d, J = 23 Hz), 114.3 (CF_3, q, J = 286 Hz), 82.6 (C), 71.7 (CH), 54.0 (C), 41.5 (C), 34.6 (CH_2), 28.6 ($3CH_3$), 27.6 ($3CH_3$), 24.7 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.7, −74.1, −111.7. IR (neat, cm^{-1}) 2979 (w), 1717 (m), 1592 (w), 1453 (m), 1369 (m), 1265 (m), 1220 (m), 1131 (s), 845 (m), 781 (m), 753 (m), 694 (m). LC−MS (ESI) compound hydrolyses to give **12h**. Crystal data: CCDC 1504396, $C_{25}H_{28}F_7NO_5$, triclinic, space group $P\bar{1}$ (no. 2), a = 9.3392(6), b = 12.0373(8), c = 25.2796(17) Å, α = 101.028(3), β = 92.592(3), γ = 111.947(3)°, V = 2565.9(3) Å^3, Z = 4, T = 120 K, R_1 = 8.55%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02346.

Crystallographic data (CCDC-1504394−1504396) (CIF)

General experimental procedures, spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) The remainder of the isolated material was identified as the enoxy trifluoroacetate intermediate and the hydrolysis product **12g** in ca. 35% yield each.

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